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EXAMINER

RAWLINGS, STEPHEN L //

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 03/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/855,342

Applicant(s)

CALIGIURI ET AL.

Examiner

Stephen L. Rawlings, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 10 October 2002 and 08 November 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 12-50 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 12-50 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5, 6. 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

1. The election without traverse filed October 10, 2002 in Paper No. 9 is acknowledged and has been entered.
2. The amendment filed November 8, 2002 in Paper No. 10 is acknowledged and has been entered. Claims 1-11 have been canceled. Claims 12 and 14-21 have been amended. Claims 22-50 have been added.
3. Claims 12-50 are pending in the application and are currently under prosecution.

***Election/Restrictions***

4. The requirement to elect a species of invention set forth in the previous Office action mailed September 10, 2002 (Paper No. 8) is withdrawn.

***Specification***

5. The specification is objected to because on page 24, in lines 4-6, it teaches that a fragment of an anti-HER2 antibody will retain the ability to bind CD20.

6. The specification is objected to because of numerous references to "the CALGB 9661 Protocol" and citations therein; see page 27. The referral to "the CALGB 9661 Protocol" and citations therein is objectionable because it cannot be ascertained if, or by what means "the CALGB 9661 Protocol" can be acquired and considered. The citations contained in "the CALGB 9661 Protocol" are not identified by any means other than reference numbers, and the nature of the cited material, whether, for example, published or unpublished, cannot be ascertained. Applicants have not provided a copy of "the CALGB 9661 Protocol"; nor has the protocol been cited on a PTO-Form 1449. Accordingly, the content of this document cannot be determined.

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

For example, the trademark Proleukin™, which is registered by Cetus Corporation, is improperly used on pages 20 and 29 in lines 5 and 2, respectively.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

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### ***Claim Objections***

8. Claims 43-46 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 18 and 38-40, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

9. Claims 12-50 are objected to because claims 12, 16, 17, and 42 recite the phrase "a cancer characterized by overexpression of the HER2 receptor protein in a subject". Recitation of this phrase is objectionable because it is not clear that the cancer is characterized by overexpression of HER2, and not by a subject in whom HER2 is overexpressed. Accordingly, it is suggested that Applicants amend claims 12, 16, 17, and 42, rewording the phrase so that the latter interpretation would not be made in determining whether another inventive entity infringes upon the metes and bounds of Applicants' claims.

10. The specification and claims 12-50 are objected to because the specification and the claims teach or recite that initial IL-2 doses typically, or preferably range from about 0.5 to about 4.0 mIU/m<sup>2</sup>, while pulse doses of IL-2 are typically, or preferably about 12 mIU/m<sup>2</sup>. The disclosures and recitations are objectionable because the Examiner firmly believes the appropriate low-dose of IL-2 more typically might range from about 0.5 to about 4.0 mIU/m<sup>2</sup>, while the appropriate pulse might more typically be about 12.0 mIU/m<sup>2</sup>, but not more than 15.0 mIU/m<sup>2</sup>.

11. Claims 15, 34, 40, and 46 are objected to because the claims recite limitations requiring the therapeutically effective dose of anti-HER2 antibody or fragment thereof to be about 4.0 mg/m<sup>2</sup>. Recitation of the limitations is objectionable, because depending upon the size and the mass of the subject the therapeutically effective dose of anti-HER2 antibody may not fall within the range of therapeutically effective doses recited in the claims from which claims 15, 34, 40, and 36 depend.

***Claim Rejections - 35 USC § 112***

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 25 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25 and 31 recite the limitation "human form thereof". However, there does not appear to be proper and sufficient antecedent basis in the as filed specification for recitation of this language in the present claims. Therefore, the recitation appears to introduce new matter and thereby violates the written description requirement set forth under 35 USC § 112, first paragraph.

This issue might be resolved if Applicants were to point to particular disclosures in the specification that are believed to provide the necessary explicit, expressive, or implicit support for the recitation of the limitation in the present claims.

14. Claims 12-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-50 are drawn to methods comprising administering to a subject interleukin-2 (IL-2) or a variant thereof. However, the specification includes only a written description of one species of the genus of IL-2 variants to which the claims refer. The written description is insufficient to meet the requirements set forth under 35 USC § 112, first paragraph because the specification fails to teach how the disclosed species, namely Proleukin™ (Aldesleukin) is representative of the genus of IL-2 variants. Given

the description of Proleukin™ alone the skilled artisan would not reasonably conclude that Applicants had possession of the claimed invention at the time the application was filed because the genus of IL-2 variants is not adequately described to enable the skilled artisan to immediately envision, or recognize at least a substantial number of members of the genus of molecules to which the claims refer.

Claims 27-31 are drawn to methods comprising administering to a subject recombinant IL-2 having an amino acid sequence for human IL-2 or a variant thereof. While Proleukin™ is a recombinant human IL-2, the specification does not describe the particular features or characteristics of human IL-2 that identify and distinguish the members of the genus of recombinant IL-2 molecules to which the claims are drawn. Moreover, the amino acid sequence of human IL-2 is not disclosed, and the specification fails to identify the features of such an amino acid sequence that would distinguish human IL-2 from any other IL-2; and therefore the written description is inadequate because given only the benefit of the disclosure, the skilled artisan could not identify human IL-2 or variants thereof.

Claims 28-31 are drawn to methods comprising administering to a subject a recombinant variant of IL-2 having at least about 70% identity to the amino acid sequence for human IL-2. However, again, the specification does not teach the amino acid sequence of human IL-2, but moreover the specification fails to teach which amino acids of the amino acid sequence of human IL-2 can be replaced or deleted, or between which amino acids additional amino acids can be inserted, or by which other amino acids replacements can be made, so the variant retains the activity of human IL-2.

MPEP § 2163.02 states, “[a]n objective standard for determining compliance with the written description requirement is, ‘does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed’ ”. The courts have decided:

The purpose of the “written description” requirement is broader than to merely explain how to “make and use”; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the “written description” inquiry, *whatever is now claimed*.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

*The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement* (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicants were in possession of the claimed genus. However, factual evidence of an actual reduction to practice of at least a substantial number of members of the claimed genus has not been disclosed by Applicants in the specification; nor have Applicants shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor have Applicants described distinguishing identifying characteristics sufficient to show that Applicants were in possession of the claimed invention at the time the application was filed.

Skolnick, et al (*Trends in Biotechnology* 18: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence

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of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in an undisclosed amino acid sequence, that a variant of human IL-2 would be found to be therapeutically effective in practicing the claimed invention. Therefore, as evidenced by the teachings of Skolnick, et al, the art is unpredictable.

The *Guidelines* state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Claims 25 and 31 are drawn to methods comprising administering to a subject a "human form" of 4D5. "4D5" designates a mouse monoclonal antibody that binds HER2; and a "human form" thereof is not well known in the art. As the specification does not describe a "human form" of 4D5, one skilled in the art would not reasonably conclude that Applicants were in possession of the claimed invention at the time the application was filed.

15. Claims 12-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ in combination with a therapeutically effective amount of Proleukin™, does not reasonably provide enablement for a method for treating a subject having a cancer that is characterized by overexpression of HER2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

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The teachings of the specification cannot be extrapolated to the enablement of the claimed invention, because the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims. For this reason, the skilled artisan could not have a reasonable expectation of success in practicing the claimed invention without having the need to perform additional, undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 12-50 are drawn to methods comprising administering to a subject interleukin-2 (IL-2) or a variant thereof. However, as evidenced by the teachings of Skolnick, et al (cited supra), the art of protein chemistry is highly unpredictable, and for this reason, the amount of guidance and direction provided in the specification is not sufficient to enable the skilled artisan to make and use a variant of IL-2 to treat cancer. Furthermore, apart from disclosing the use of Proleukin™, the specification does not exemplify the use of any other species of the genus of IL-2 molecules to which the claims refer. *In re Fisher*, 166 USPQ 18 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different biological and pharmacological activities. Although claims 28-31 recite a limitation requiring the recombinant IL-2 of claim 12 to have an amino acid sequence that is at least about 70% identical to the amino acid sequence of human IL-2, the specification does not teach the amino acid sequence of human IL-2. Moreover, the specification fails to teach which amino acids of the amino acid sequence of human IL-2 can be replaced or deleted, or between which amino acids additional amino acids can be inserted, or by which other amino

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acids replacements can be made, so the variant retains the activity of human IL-2. Given that the skilled artisan cannot predict which variants of human IL-2 will retain the function of human IL-2, or of Proleukin™, in the absence of sufficient guidance and direction, the skilled artisan could not make and use at least a substantial number of members of the genus of IL-2 molecules to which the claims refer without having the need to perform additional, undue experimentation.

Claims 12-50 encompass methods comprising administering to a subject a fragment of an antibody that binds HER2; however, many fragments of such an antibody would not be reasonably expected to be therapeutically useful, especially if the fragment does not retain the binding specificity of the antibody. The fragment of the antibody must retain the ability of the antibody to bind HER2 to be effective, absent any teaching to the contrary, and therefore the claims should be so limited.

In addition, claims 12-50 encompass methods comprising administering to a subject an antibody that binds a non-extracellular domain of HER2. However, it appears that no antibodies that bind the intracellular domain, for example, of HER2 have been found therapeutically useful, as there is no factual evidence that suggests otherwise, which is disclosed by Applicants' or known in the art. As the specification does not teach an antibody that binds the intracellular domain of HER2, which can be used to successfully practice the claimed invention, the breadth of the claims appears to be a mere invitation to the artisan to develop such an embodiment of the invention. Even if an antibody that binds the intracellular domain of HER2 were found to inhibit the growth of tumor cells that overexpress HER2, the means by which such an antibody can be delivered to the tumor cells *in vivo* has not been addressed in the specification. In *Colbert v. Lofdahl*, 21 USPQ2d, 1068, 1071 (BPAI 1992), the court concluded, "[i]t is not sufficient to define the recombinant molecule by its principal biological activity, e.g., having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property."

Nevertheless, the specification describes two species of anti-HER2 antibodies that bind the extracellular domain of HER2 with which it is asserted that the claimed invention can be practiced with a reasonable expectation of success. However, the

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prior art teaches that although an antibody binds HER2, the antibody is not necessarily capable of inhibiting the growth of cancer cells that express HER2 at the cell surface. For example, Stancovski, et al (*Proceedings of the National Academy of Science USA* **88**: 8691-8695, 1991) teach that at least one anti-HER2 antibody actually promotes tumor growth (page 8693, column 1). Similarly, Lewis, et al (*Cancer Immunology & Immunotherapy* **37**: 255-263, 1993) found that an antibody that binds HER2 promotes the growth of tumor cells. Therefore, it appears that merely teaching the artisan to make an antibody that binds specifically to HER2 would be insufficient to enable the skilled artisan to make an anti-HER2 antibody that upon administering to a subject, is capable of inhibiting the growth of subject's tumor cells that abnormally express a relative abundance of HER2 at the cell surface.

In light of the prior art, it appears only antibodies that bind a few particular epitopes of the extracellular domain of HER2 are capable of inhibiting the growth of tumor cells. While US Patent No. 5,772,997-A does not disclose anti-HER2 antibodies that promote the growth of breast cancer cells, as did some of the antibodies, Hudziak, et al do disclose that the growth inhibitory properties of monoclonal antibody 4D5 are somewhat unique, as other anti-HER2 antibodies were found to inhibit the growth of the cells to a lesser extent, or not at all.

Claims 12-50 are drawn to methods for treating cancer, but the specification discloses that only patients having breast cancer responded positively to treatment with exemplified embodiment of the invention. Furthermore, the prior art teaches that monoclonal antibody 4D5 cannot always be used effectively. For example, Lewis, et al (cited *supra*) teach mouse monoclonal antibody 4D5 does not affect the proliferation of gastric and colon cancer cells, even though the cells express an amount of HER2 that is equivalent to the amount expressed by breast cancer cells that are sensitive to the effects of treatment with the antibody. Accordingly, it appears that teaching the artisan to select subjects having a cancer that overexpresses HER2 is insufficient to guide the successful application of the claimed invention. In view of Applicants' disclosure and of the prior art, the skilled artisan would not accept the assertion that the claimed invention

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can be used with a reasonable expectation of success to treat any type of cancer that overexpresses HER2 without the need to perform additional, undue experimentation.

Additionally, it appears that Applicants invention was conceived upon Applicants' finding that IL-2 enhances the cytotoxicity of at least some effector cells, e.g., natural killer cells, monocytes, macrophages, etc., capable of mediating antibody-dependent cell cytotoxicity (ADCC) in the presence of Herceptin™, but not in its absence, since breast cancer cells that express HER2 were found to be susceptible to the effects of the IL-2-activated natural killer cells, and breast cancer cells that do not express HER2 were not. Therefore, it appears that any greater effectiveness of the combination of Herceptin™ and Proleukin™ would depend upon the ability of the antibody to mediate ADCC; otherwise, the presence of IL-2-activated effector cells would not be expected to enhance the antiproliferative, i.e., therapeutic, effect of an anti-HER2 antibody. As so, while the recombinant humanized version of the murine monoclonal antibody 4D5, namely Herceptin™ has been shown to mediate ADCC, it is noted that Lewis, et al (cited *supra*) teach that the murine monoclonal antibody does not mediate ADCC, and is further incapable of fixing complement to mediate complement-mediated cell cytotoxicity, which suggests that the murine antibody cannot be used with a reasonable expectation of success in practicing the claimed method. On the other hand, even though mouse monoclonal anti-HER2 antibody 520C9 has been reported to mediate ADCC, Stancovski, et al (cited *supra*) disclose that of mouse anti-HER2 antibodies found to inhibit the growth of tumor cells, none were found to mediate ADCC, suggesting that the mechanism by which mouse anti-HER2 antibodies typically affect the proliferation of cells is not effector cell dependent, and further suggesting that monoclonal antibody 520C9 is unusual in its ability to mediate ADCC.

In view of the prior art, then, the disclosure would not be sufficient to enable the skilled artisan to make a non-recombinant or engineered antibody that can be used with a reasonable expectation of success to practice the claimed invention without the need to perform additional, undue experimentation, because seldom would a mouse anti-HER2 antibody be expected to be capable of mediating ADCC, and the specification

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fails to describe methods by which such antibodies might be easily identified. It follows that the disclosure would be insufficient to enable the skilled artisan to use the claimed invention without having the need to first perform additional, undue experimentation in order to have a reasonable expectation of success in doing so. Even though monoclonal antibody 520C9 is capable of mediating ADCC, the embodiment in which the monoclonal antibody is used has not been exemplified. The art teaches that a bispecific recombinant antibody comprising an antigen-binding fragment of the monoclonal antibody can be used to inhibit the growth of tumor cells. The art teaches that an immunotoxin comprising the antibody can be used to inhibit the growth of tumor cells, but the art does not teach that the monoclonal antibody itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. In fact, Keler, et al (*Cancer Research* **57**: 4008-4014, 1997) demonstrate the F(ab')<sub>2</sub> fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9. However, the claims are not limited to methods comprising administering to a subject an a bispecific antibody capable of mediating ADCC, or an immunotoxin comprising at least an antigen-binding fragment of monoclonal antibody; and considering the state of the art, and its unpredictable nature, the skilled artisan would not accept the assertion that the claimed invention can be used to effectively treat cancer in the absence of working exemplification that is reasonably commensurate in scope with the claims.

Finally, claims 13-15, 32-40, and 44-46 further limit the scope of the terms "therapeutically effective dose of IL-2 or variant thereof" and "therapeutically effective dose of anti-HER2 antibody or fragment thereof" from the scope of the claims from which they depend. However, it does not appear that the specification provides guidance as to when the different embodiments should, or should not be practiced, since the specification does not teach or exemplify how the most appropriate doses, or ranges thereof should be selected, or upon what criteria. For example, given only the benefit of Applicants' disclosure, the practitioner could not know which of the therapeutically effective doses of IL-2 and anti-HER2 antibody should be administered to a particular patient in need of treatment. Therefore, the skilled artisan could not have

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a reasonable expectation of successfully practicing each of the claimed methods, as it would be reasonably expected that at least a few of the claimed methods could not be used to efficaciously treat the patient at hand. Since the specification does not provide guidance or direction as to how the practitioner might select which of the claimed methods should be practiced with which patients, the claimed methods could be practiced with a reasonable expectation of success without having the need to first perform additional, and an undue amount of experimentation.

16. The specification is objected to and claims 24, 25, 30, and 31 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

It is unclear if cell lines that produce an antibody having the exact structural and chemical identity of the monoclonal antibodies to which the claims refer are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing a monoclonal antibody to which the claims refer, it would not be possible to practice the claimed invention, because it would not be possible to make the monoclonal antibody. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different  $V_H$  chains (about 50% homologous) can combine with the same  $V_K$  chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different  $V_H$  sequences combine with different  $V_K$  sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and

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out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (Fundamental Immunology, 3<sup>rd</sup> ed., William E. Paul, M.D. ed., 1993, page 242). Therefore, it would require undue experimentation to reproduce the claimed antibody. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809).

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP § 1.804(b).

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***Claim Rejections - 35 USC §§ 102 and/or 103***

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

19. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

20. Claims 12-19, 24, 26-28, 30, 32-40, and 42-47 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent Nos. 4,863,726-A or 4,894,227-A.

US Patent Nos. 4,863,726-A ('726) and 4,894,227-A ('227) teach a method for treating breast cancer comprising administering to a subject a combination of a therapeutically effective amount of a recombinant human IL-2 (which is now marketed

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under the tradename Proleukin™) and a therapeutically effective amount of an anti-HER2 antibody, namely 520C9 (Example II).

'726 and '227 teach that IL-2 and the antibody can be made into a sterile, stable lyophilized formulation. '726 and '227 teach the agents can be reconstituted and administered to the subject concurrently, simultaneously or sequentially, by subcutaneous injection. '726 and '227 teach that the regimen can comprise multiple dosing of one or both agents; '726 and '227 exemplify administering the agents daily for periods of 7 or 14 days, depending upon the agent, but teach, "[t]he dosage and scheduling must be adjusted to obtain efficacious results" (column 25, lines 48 and 49).

'726 and '227 teach, "combinations of drugs are administered in an attempt to obtain a synergistic cytotoxic effect on most cancers" (column 2, lines 54-56). Moreover, '726 and '227 disclose, "administration of the combination of agents [...] is expected to reduce tumor growth greater than the administration of either agent alone" (column 25, lines 38-41).

Although '726 and '227 do not explicitly teach that a therapeutically effective dose of IL-2 is the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg, '726 nor '227 do provide guidance indicating that the therapeutically effective dose must be sufficient "to achieve some tumor reduction or augmentation of LAK [lymphokine-activated killer] activity" (column 6, lines 25-27). In column 6, '726 and '227 further disclose:

The dose and dosage regimen will depend on whether the IL-2 and immunotoxin(s) [, i.e., antibodies conjugated to cytotoxic moieties,] are being administered separately or as a mixture, the type of immunotoxin(s) and cancer, the patient/host and the patient's history.

If multiple doses are employed, [...] the frequency of administration will depend, for example, on the type of component, cancer, dosage amounts, host, etc. For some types of cancers, daily administration may be effective, whereas for other types of cancer, administration every other day or every third day may be effective, but daily administration ineffective. The practitioner will be able to ascertain from clinical trials which route of administration and frequency of administration are most effective in humans in any particular case.

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In addition, '726 and '227 exemplify the method of treatment in Examples II and III, wherein slightly different protocols are were used to demonstrate the efficacy of the method, but using mice as models. The skilled artisan could extrapolate, if need be, as '726 and '227 disclose that various modifications of the method will be apparent to those skilled in the art, so that the disclosures provide sufficient guidance to enable the skilled artisan to practice the invention in cases where the subject is a human. This is evidenced, for example, by claim 11 of '726.

However, if '726 and '227 are not clearly anticipatory of the claimed invention, particularly since '726 and '227 do not explicitly teach that a therapeutically effective dose of IL-2 is the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg, any necessary or appropriate modification of the methods of '726 and '227, which would be guided by the disclosures, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

21. Claims 12-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Nos. 4,863,726-A or 4,894,227-A in view of Hank, et al (Cancer Research 50: 5234-5239, 1990) and Keler, et al (Cancer Research 57: 4008-4014, 1997), or Silwowski, et al (Seminars in Oncology 26: 60-70, 1999) and Lewis, et al (Cancer Immunology & Immunotherapy 37: 255-263, 1993), and in further view of Meropol, et al (Cancer Immunology & Immunotherapy 46: 318-326, 1998).

US Patent Nos. 4,863,726-A ('726) and 4,894,227-A ('227) teach that which is set forth in the rejection above.

However, neither '726 nor '227 disclose that the antibody can be a recombinant antibody, such as a humanized antibody, or a chimeric antibody that comprises at least one human constant region.

Additionally, neither '726 nor '227 explicitly teach the anti-HER2 antibody can be the mouse monoclonal antibody 4D5 or a recombinant version thereof.

Finally, neither '726 nor '227 teach that the treatment regimen can or should comprise intermediate-dose IL-2 pulsing.

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Nevertheless, Hank, et al teach, "[m]onoclonal antibodies (mAB) with tumor specificity are able to enhance the immunological specificity of interleukin 2 (IL-2)-activated lymphokine activated killer (LAK) cells" (abstract). In the abstract, Hank, et al further disclose:

When peripheral blood mononuclear cells were obtained from cancer patients prior to and following in vivo therapy with interleukin 2, a significant increase was noted in ADCC activity by peripheral blood mononuclear cells obtained following IL-2 therapy. Inclusion of IL-2 in the medium during the cytotoxic assay with mAB further boosted ADCC. The total activity seen was often greater than the sum of the independent LAK activity and standard ADCC activity. The cells responsible for this ADCC had the CD16+ Fc receptor.

Hank, et al teach, "[o]ur experiments document that murine mAB are capable of directing tumor specific ADCC which is much more potent with PBM [peripheral blood mononuclear cells] obtained from patients following continuous infusion therapy with IL-2" (page 5238, column 1). In addition, Hank, et al speculate, "where mAB able to mediate ADCC proved ineffective, it is possible that inadequate effector function due to inefficient ability of patients' cells mediate ADCC was a limiting factor" and "[t]he in vivo activation of effector cells with IL-2 combined with mAB that mediate ADCC may overcome this limitation" (page 5238, column 2). Hank, et al conclude, "[c]ombining IL-2 with mAB in clinical therapy may lead to a wider range of tumor types being responsive to immunotherapy and may also enhance the efficacy of therapy by specifically targeting activated effector cells to tumor cells recognized by mAB" (abstract).

Keler, et al teach a bispecific antibody designated MDX-H210, which comprises chemically linked Fab' fragments isolated from a humanized version of monoclonal antibody 22, which binds an epitope of Fc $\gamma$ RI (CD64), and monoclonal antibody 520C9, which is one of the anti-HER2 antibody to which the claims specifically refer. Keler, et al disclose the antibody "was developed to target cytotoxic effector cells expressing Fc $\gamma$  receptor type I (Fc $\gamma$ RI, CD64) to HER2/*neu*-overexpressing tumor cells" (abstract). Keler, et al suggest the in vivo cytotoxic potential of MDX-H210 may be enhanced by combination therapy with cytokines.

Furthermore, Silwowski, et al and Lewis, et al teach a chimeric version and a humanized version of anti-HER2 mouse monoclonal antibody 4D5. Silwowski, et al

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and Lewis, et al teach both antibodies were produced "to provide the potential for antibody-mediated cytotoxic activity" (Lewis, et al, abstract). Lewis, et al disclose that both antibodies elicited ADCC responses in accordance with the level at which HER2 is expressed by the targeted cells. Silwowski, et al disclose the humanized antibody, which is generically designated trastuzumab and marketed under the tradename Herceptin™, was found to be very effective against tumor cells that overexpress HER2. While trastuzumab may inhibit the growth of tumor cells by more than one mechanism, Silwowski, et al teach the mediation of antibody-dependent cytotoxicity of the tumor cells by human peripheral blood mononuclear cells pretreated with IL-2 is alone very effective. Silwowski, et al disclose that both natural killer cells and monocytes are "extremely potent in killing trastuzumab-coated target cells", and speculate this potency is due to "the near-irreversible binding of trastuzumab to cells that overexpress HER2" (page 67, column 1).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat breast cancer characterized by overexpression of HER2 by concurrently administering to the subject having the cancer a therapeutically effective combination of recombinant human IL-2 and an anti-HER2 antibody, namely a chimeric or humanized recombinant form of the mouse monoclonal antibody 4D5, or alternatively of the mouse monoclonal antibody 520C9. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art to administer to the subject a therapeutically effective dose of IL-2 in the range of about 0.5 to about 4.0 mIU/m<sup>2</sup> and a therapeutically effective dose of the antibody in the range of about 1.0 to about 10.0 mg/kg, where and when appropriate, depending upon the results of clinical trials establishing the most efficacious regimens of treatment for select individuals characterized by a number of criteria, including the predetermined level of acceptable toxicity, the effectiveness, the type and stage of the cancer, etc. Thus, in some cases, it would be *prima facie* obvious to one of ordinary skill in the art to administer, for example, a dose of anti-HER2 antibody in the range of about 3.0 to about 8.0 mg/kg of the subject, whereas in another case, it would be *prima facie* obvious to administer a dose of anti-HER2 antibody of about 4.0 mg/kg. Similarly, it would be *prima facie*

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obvious to administer, for example, a dose of IL-2 in the range of about 0.5 to 4.0 mIU/m<sup>2</sup>, where and when appropriately indicated. Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art to administer to the subject therapeutically effective doses of IL-2 and antibody according to a predetermined schedule established in clinical trials as the providing the greatest efficacy in select individuals. Nevertheless, the teachings of the prior art would have provided at least the suggestion that an initial dose of IL-2 be administered simultaneously, if not before administering an initial dose of the antibody, since, for example, Hank, et al speculate that the effectiveness of an antibody capable of mediating ADCC is dependent upon the activation state of the subjects' effector cells. Given the teachings of the prior art, daily administration of IL-2 would then be expected to maintain the pool of activated effector cells until and after the antibody is administered to the subject. The reasonable expectation of success, which is made evident by the teachings of the prior art, would have provided the artisan of ordinary skill in the art at the time the invention was made with sufficient motivation to have done so.

While none of the cited reference discussed in the paragraphs above teach a regimen comprising intermediate-dose IL-2 pulsing, Meropol, et al teach that the inclusion of intermediate-dose IL-2 pulsing is well tolerated on an out-patient basis and overcomes the limitations of continuous low-dose IL-2 infusions, because an IL-2 concentration in the patient can be achieved, which is sufficient to engage a significant portion of the IL-2R $\beta\gamma$  complexes present on an expanded population of natural killer cells to better maintain an activated state. Meropol, et al disclose the maximum tolerated pulse dose of IL-2 was found to be 15 MIU/m<sup>2</sup>; and the highest, best tolerated dose was found to be 12 MIU/m<sup>2</sup>. Meropol, et al teach that a three-day pulse can be used effectively after an initial low-dose cycle of about 1.25 MIU/m<sup>2</sup> and can be repeated about every two weeks. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to further modify the regimen that would have been obvious, given the teachings of the other references, to include intermediate-dose pulsing of IL-2, where the intermediate dose is about 12 MIU/m<sup>2</sup>. Again, the reasonable expectation of success, which is made evident by the teachings of the prior art, would

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have provided the artisan of ordinary skill in the art at the time the invention was made with sufficient motivation to have done so.

**Conclusion**

22. No claims are allowed.


23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.  
Examiner  
Art Unit 1642

slr  
January 25, 2003

  
ANTHONY C. CAPUTA  
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